Wrist actigraphy predicts outcome in patients with pulmonary hypertension

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Abstract: Background: Pulmonary hypertension (PH) impairs quality of life, exercise performance and survival. Simple measures to monitor the disease are needed. Objectives: We tested whether actigraphy by a wrist-worn device in the patient's home reflects disease severity in PH patients. Methods: Twenty-three outpatients with pulmonary arterial and chronic thromboembolic PH (15 females), functional classes II-IV, underwent clinical examination and actigraphy over 2 weeks while pursuing their usual life at home. Actigraphies were correlated with clinical data and mean pulmonary artery pressure (mPAP). Deaths, lung transplantations and pulmonary endarterectomy were recorded over 4 years. Results: Actigraphies revealed a mean ± SD daytime activity duration of 14:57 ± 1:14 h with 146 ± 125 activity counts/min. Very severely impaired patients (mPAP 50 ± 7 mm Hg) were inactive for longer periods at night (8:25 ± 1:18 h) and less active during the day (54 ± 44 counts/min) when compared to modestly impaired patients (mPAP 33 ± 7 mm Hg; inactive at night for 6:58 ± 0:39 h; daytime activity 229 ± 148 counts/min, $p < 0.05$ in all instances). Out of 19 patients followed for 4 years, 5 died and 1 received a lung transplantation. Kaplan-Meier analysis revealed a shorter survival without lung transplantation in patients with a duration of daytime activity of <15 h/day than those with >15 h/day duration (log rank, $p = 0.026$). Conclusion: A long nocturnal rest and reduced daytime activity recorded by actigraphy are associated with severe hemodynamic impairment and reduced survival in patients with PH. Therefore, wrist actigraphy performed during everyday life in the patient's home holds promise as a simple tool for the assessment of disease severity and prognosis in patients with PH.

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Wrist Actigraphy Predicts Outcome in Patients with Pulmonary Hypertension

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Key Words

Pulmonary hypertension · Actigraphy · Mean pulmonary artery pressure

Abstract

Background: Pulmonary hypertension (PH) impairs quality of life, exercise performance and survival. Simple measures to monitor the disease are needed. ***Objectives:*** We tested whether actigraphy by a wrist-worn device in the patient's home reflects disease severity in PH patients. ***Methods:*** Twenty-three outpatients with pulmonary arterial and chronic thromboembolic PH (15 females), functional classes II–IV, underwent clinical examination and actigraphy over 2 weeks while pursuing their usual life at home. Actigraphies were correlated with clinical data and mean pulmonary artery pressure (mPAP). Deaths, lung transplantations and pulmonary endarterectomy were recorded over 4 years. ***Results:*** Actigraphies revealed a mean ± SD daytime activity duration of 14:57 ± 1:14 h with 146 ± 125 activity counts/min. Very severely impaired patients (mPAP 50 ± 7 mm Hg) were inactive for longer periods at night (8:25 ± 1:18 h) and less active during the day (54 ± 44 counts/min) when compared to modestly impaired patients (mPAP 33 ± 7 mm Hg; inactive at night for 6:58 ± 0:39 h; daytime activity 229 ± 148 counts/min, $p < 0.05$ in all instances). Out of 19 patients followed for 4 years, 5 died and 1 received a lung transplantation. Kaplan-Meier analysis revealed a shorter survival without lung transplantation in patients with a duration of daytime activity of <15 h/day than those with >15 h/day duration (log rank, $p = 0.026$). ***Conclusion:*** A long nocturnal rest and reduced daytime activity recorded by actigraphy are associated with severe hemodynamic impairment and reduced survival in patients with PH. Therefore, wrist actigraphy performed during everyday life in the patient's home holds promise as a simple tool for the assessment of disease severity and prognosis in patients with PH.

Introduction

Pulmonary hypertension (PH) is a severe condition leading to progressive right heart failure with impaired quality of life, reduced exercise capacity and premature death. Two major groups of PH include pulmonary arterial hypertension, which is either idiopathic or associated

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with different conditions, and chronic thromboembolic PH, i.e. groups 1 and 4 according to the Dana Point Classification [1]. An increasing number of therapeutic agents including prostanoids, endothelin receptor antagonists and phosphodiesterase-5 inhibitors have been shown to be effective in pulmonary arterial and inoperable chronic thromboembolic PH [2–6]. Pulmonary endarterectomy is the treatment of choice in suitable candidates with chronic thromboembolic PH [7, 8]. Despite advances in therapies, PH is still incurable; intense research on new therapeutics is therefore ongoing. PH affects many domains of the daily life of an individual such as participation in social activities, work, recreation and household tasks. Some of these aspects can be evaluated by questionnaires and by symptom scales such as the WHO functional class. However, questionnaire evaluations are confounded by a high inter- and intraindividual variability. Therefore, there is a need for objective assessment of the clinical course and response to treatment in PH patients. Repeated right-heart catheterization is not practical because of its invasive nature and Doppler echocardiography lacks precision. Measurement of the exercise performance by spiroergometry and the 6-min walk test (6MWT) can provide valuable information, but the results are susceptible to movement and skeletal muscle limitations. Moreover, a single test performed in a physician's office may not represent an individual's performance in everyday life.

An actigraph placed on the wrist like a watch enables a continuous record of movements to be kept during the usual everyday activities of the patients in their home over prolonged periods of time (from days to weeks). Actigraphy is used to measure periods of rest as surrogates of sleep and to quantify activity during wakefulness in a variety of patient groups [9–12]. The technique is simple to use and unobtrusive. We reasoned that actigraphy might complement the self-reports and clinical assessment of PH patients, thereby increasing our understanding of limitation in activity and disability in PH. The purpose of this study was to perform actigraphy in PH patients and to correlate the results with questionnaire assessments, exercise capacity, sleep studies and outcome. Compared to patients with mild PH, patients with more severe hemodynamic compromise display reduced physical activity, and some are confined to their homes and have a poor prognosis [13]. We tested the hypothesis that daytime activity measured by wrist actigraphy in patients with pulmonary arterial or chronic thromboembolic PH is correlated with the severity of PH assessed by right-heart catheter and survival.

Material and Methods

Patients

Consecutive patients with PH classified as being either pulmonary arterial or chronic thromboembolic were asked to participate [14]. PH was defined according to WHO classification and patients were included if PH was idiopathic or associated with collagen vascular, congenital heart or chronic thromboembolic disease [1]. Patients were in a stable condition on the same medication for >4 weeks. The study was approved by our ethical board and all patients gave their written informed consent.

General Baseline Assessments

Patients were physically examined; current medication and functional class were noted. Questionnaire evaluation included quality of life [short-form (SF)-36 questionnaires] [15, 16] and sleepiness by the Epworth scale [17]. A 6MWT was performed. Hemodynamic data from the last right-heart catheterization were noted. PH was grouped according to hemodynamics in modest [mean pulmonary artery pressure (mPAP) = 26–39 mm Hg], severe (mPAP ≥40) and very severe (mPAP ≥40 with mixed venous oxygen saturation <60%) [18]. Venous N-terminal pro-brain natriuretic peptide (NT-proBNP) was measured [19, 20]. Sleep studies were performed as previously described [14].

Actigraphy

Patients wore an actigraph (Actiwatch® Model AW4, Neurotechnology Ltd., Cambridge, UK) on their nondominant wrist for 2 weeks. They were instructed to press a marker button on the actigraph when they went to bed in the evening and got up in the morning. They recorded their bedtime, the time they got up in the morning and any special events in a diary. Data stored in the internal memory of the actigraph were downloaded into a computer for analysis.

The Actiwatch actigraph measures activity with a piezoelectric accelerometer that records amounts, duration and intensity of movements in all directions at a sampling rate of 32 Hz. Accelerations over 0.05 *g* are recorded and their sum during consecutive epochs of 1 min is stored in the internal memory of the actigraph.

Actigraphic data were analyzed with commercially available software (sleep analysis V 7.2). The following data were obtained: time in bed, estimated total sleep time (time with inactivity during time in bed), sleep efficiency (ratio of estimated total sleep time to time in bed) and sleep fragmentation index (number of short immobility phases ≤1 min divided by the number of uninterrupted immobility phases lasting for >1 min). Daytime activity duration was defined as the time with activity between the first phase of activity after arising and the last phase of activity before bedtime. Counts per phase of activity during the day were calculated. Naps were defined as periods with inactivity during the day.

Follow-Up

Patients were followed up at our clinic half-yearly during the first year and thereafter yearly over at least 4 years following the initial evaluation. Regular assessments included a clinical examination, a 6MWT and whatever other examinations were clinically indicated. The dates of death and lung transplantation were recorded. The cause of death was determined by contacting the physicians involved in the care of the patients and by reviewing the medical records.

Data Analysis and Statistics

We compared means using the Mann-Whitney rank-sum test, ANOVA and the Fisher test as appropriate. Correlation analysis was with the Pearson correlation and linear regression. The Kaplan-Meier analysis of transplantation-free survival was performed and potential predictors of survival were evaluated by multivariate Cox regression models. Statistical significance was accepted as $p < 0.05$.

Results

Patients

Table 1 shows the characteristics of the 23 study participants. Thirteen patients suffered from pulmonary arterial and 10 from chronic thromboembolic PH. Patients were in WHO functional classes II–IV, had a decreased 6MWT, and an elevated proBNP. They were on stable therapy with bosentan [13], sildenafil [13] and inhaled iloprost [5] for 17 ± 14 months; 9 had combination therapy. In 4 eligible patients with chronic thromboembolic disease, pulmonary endarterectomy was performed 11 ± 12 months after actigraphy. Eleven of the 23 patients had an elevated apnea/hypopnea index >10/h mainly due to central events (table 1). Overnight oximetry revealed that patients spent an average of 33% of their time in bed with a low oxygen saturation <90%.

Table 1. Patient characteristics

Number of patients; females/males	23; 15/8
Age, years	58 ± 16
Classification of PH	
Idiopathic	11 (48)
Connective tissue disease	2 (9)
Chronic thromboembolic	10 (43)
WHO functional class II/III/IV	10/8/5 (43/35/22)
BMI	25 ± 3
Mean pulmonary arterial pressure, mm Hg	43 ± 10
Pulmonary vascular resistance, dyn•s•cm^{-5}	720 ± 303
Cardiac index, l/min/m^2	2.3 ± 0.7
NT-proBNP, ng/l (normal value <130)	1,579 ± 3,181
6-min walking distance, m	508 ± 115
Apnea/hypopnea index total, events/h	12 ± 11
Obstructive	2 ± 5
Central	10 ± 8
Mean nocturnal oxygen saturation, %	90.1 ± 3.4
Time spent with oxygen saturation <90% in % of time in bed	33 ± 36
SF-36 quality of life	
Physical component summary score	34 ± 10
Mental component summary score	49 ± 11
Epworth sleepiness score	7.5 ± 5

Values are n (%) or means ± SD. Epworth score ranges from 0–24 with ≥11 points considered excessive sleepiness. SF-36 = Short form of the medical outcome questionnaire, presented as transformed scores; lower values correspond to poorer quality of life.

Actigraphy

The typical actigraphy patterns of a patient with moderate PH and of a patient with severe PH are shown in figure 1. Table 2 provides summary statistics of actigraphic data. The average time in bed was 7:32 ± 1:05 h with a sleep efficiency of 92 ± 9% (table 2). Actigraphic measures reflecting sleep disruption, i.e. sleep efficiency and the fragmentation index, were correlated with overnight oxygen saturation ($r = 0.496$, $p = 0.019$ and $r = -0.530$, $p = 0.011$) and with subjective sleepiness assessed by the Epworth sleepiness score ($r = -0.438$, $p = 0.041$ and $r = 0.511$, $p = 0.015$). Women had a significantly longer nap time than men (17.4 ± 7.1 vs. 12.4 ± 3.2 min, $p = 0.027$). Patients with chronic thromboembolic PH had significantly less activity counts/phases at baseline compared to patients with pulmonary arterial hypertension (186 ± 136 vs. 81 ± 70, $p = 0.04$) although they did not differ from the other patients with regard to hemodynamics, 6-min walk distance or quality of life measures (data not shown).

Table 2. Actigraphy data (means ± SD)

Actigraphy on wrist, days	15 ± 2
Time in bed, h	7:32 ± 1:05
Sleep efficiency, %	91 ± 9
Sleep fragmentation index	27 ± 13
Daytime activity duration, h	14:57 ± 1:10
Total daytime activity count, $\times 10^4$	12.9 ± 11.1
Average daytime activity, counts/min	146 ± 125
Daily naps, n	3.6 ± 3.6
Total nap duration, h	1:10 ± 1:13

Actigraphy in Patients with Different PH Severities

In table 3, patients are grouped according to PH severity. Daytime activity expressed in total counts and counts per 1-min phase decreased with PH severity ($p = 0.026$ and 0.019, respectively). Individual times in bed were significantly correlated with the pulmonary vascular resistance ($r = 0.515$, $p = 0.017$). Daytime activity duration and counts/phases were associated with increased quality of life (SF-36 questionnaire on general health and vitality; $r = -0.557$, $p = 0.006$ and $r = 0.507$, $p = 0.022$).

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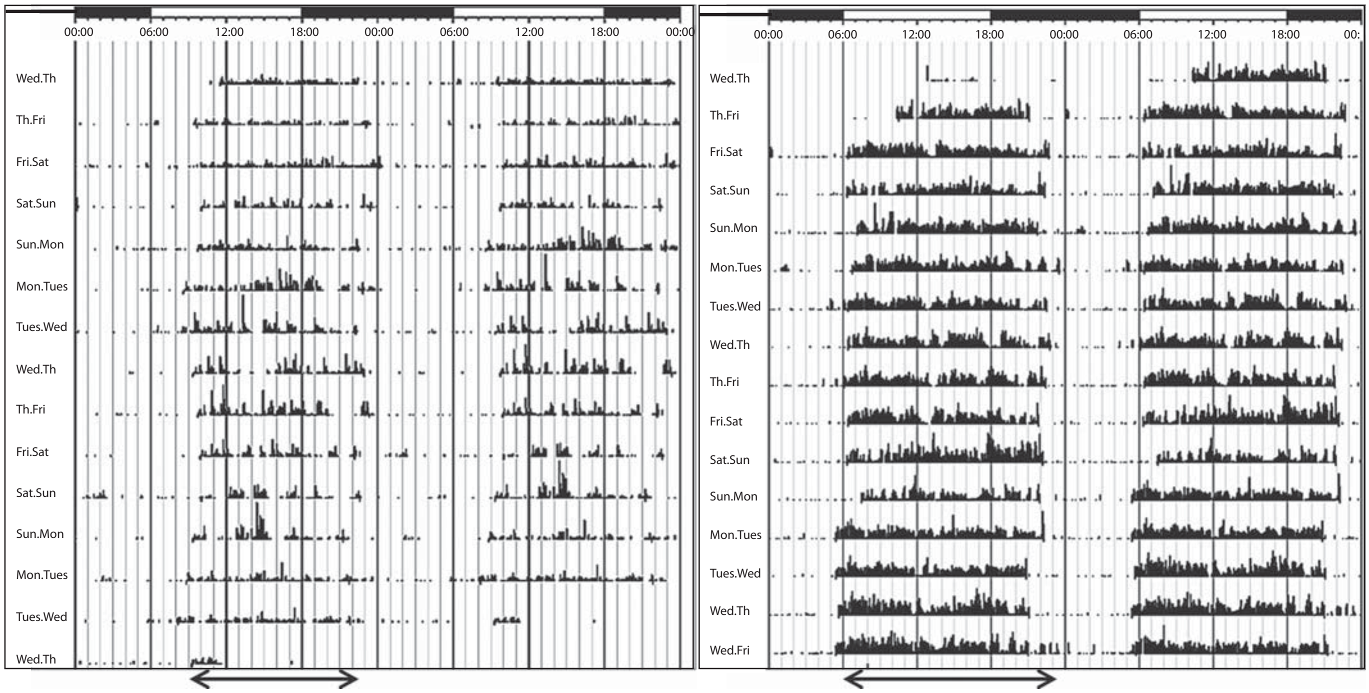

Fig. 1. Examples of day by day activity profiles (double plot, 2 × 24 h per line) for a patient with low daily activity (left panel, mPAP 46 mm Hg, mixed venous oxygen saturation 37%) and a patient with high daily activity (right panel, mPAP 37 mm Hg, mixed venous oxygen saturation 62%). The arrows illustrate the average daily activity duration and highlight the reduced activity in severe PH (left). Fri = Friday; Mon = Monday; Sat = Saturday; Sun = Sunday; Th = Thursday; Tues = Tuesday; Wed = Wednesday.

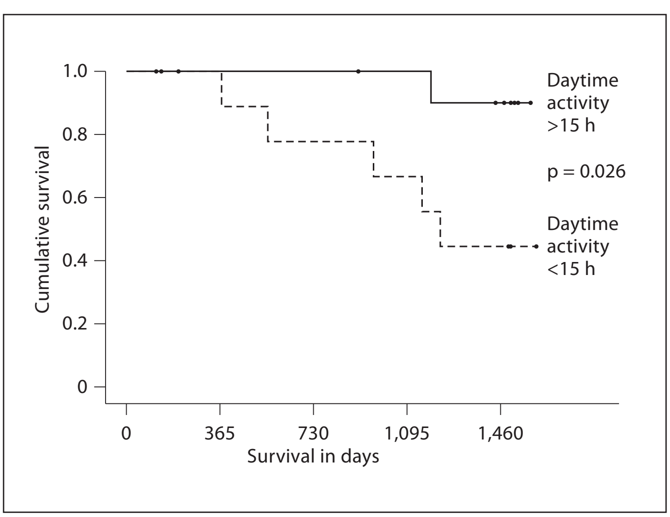

Fig. 2. Kaplan-Meier cumulative survival curves are shown for 19 patients with PH. Patients with an average daily activity time greater than 15 h (solid line) survived significantly longer without pulmonary transplantation than patients with a daily activity of less than 15 h (dashed line).

Follow-Up

Operable patients with chronic thromboembolic PH underwent pulmonary endarterectomy within a few months after baseline and were excluded from the survival analysis because the indication for surgery is not exclusively determined by disease severity. During the 4-year follow-up of the 19 PH patients, 1 underwent a lung transplantation and 5 died. All 5 died due to progressive PH leading to terminal right-heart failure; coronary artery or left-heart disease or other comorbidities that significantly altered the functional status or caused death were not diagnosed or suspected in any of the cases. Survival without lung transplantation after 1, 2, 3 and 4 years was 100, 89, 84 and 68%, respectively. Further exploratory analyses by Kaplan-Meier statistics revealed that transplantation-free survival was significantly shorter in patients with a median of <15 h daytime activity than in those with >15 h daytime activity (fig. 2, p = 0.026). Multivariate Cox regression analysis confirmed that a short duration of daytime activity was associated with a poor prognosis (hazard ratio 0.978 and 95% confidence interval 0.959–0.997, p = 0.025). In other words, for each minute a patient was active during the day, his or her hazard

Table 3. Characteristics and actigraphy of patients with different severities of PH (means ± SD)

Characteristics	Modest (n = 9)	Severe (n = 8)	Very severe (n = 6)	p
Age, years	65 ± 15	49 ± 15	59 ± 14	n.s.
6-min walking distance, m	532 ± 95	510 ± 135	470 ± 124[1], *	0.622
WHO functional class II/III/IV, n	5/4/0	4/3/1	1/1/4	
Mean pulmonary arterial pressure, mm Hg	33 ± 7	49 ± 6	50 ± 7*	<0.001
Mixed venous oxygen saturation, %	63 ± 4	67 ± 5	47 ± 8*, **	<0.001
Pulmonary vascular resistance, dyn•s•cm^{-5}	472 ± 148	781 ± 200	980 ± 321*, **	0.002
NT-proBNP, ng/l	448 ± 178	963 ± 1,055	3,915 ± 5,592	0.082
SF-36 quality of life				
Physical component summary score	37 ± 12	34 ± 8	30 ± 9	n.s.
Mental component summary score	49 ± 12	52 ± 12	47 ± 9	n.s.
Actigraphy				
Sleep time, h	6:58 ± 0:39	7:35 ± 0:50	8:25 ± 1:18	0.026
Sleep efficiency, %	88 ± 12	93 ± 5	95 ± 4	n.s.
Sleep fragmentation index	30 ± 19	26 ± 9	23 ± 6	n.s.
Daytime activity duration, h	15:06 ± 1:31	15:07 ± 0:46	14:12 ± 0:49	n.s.
Daytime activity counts, $\times 10^4$	21 ± 13	11 ± 7	4.5 ± 3.7*	0.026
Daytime activity, counts/min	229 ± 148	119 ± 13	54 ± 44*	0.026
Daily naps, n	3.2 ± 2	2.6 ± 3.9	6.1 ± 5.3	n.s.
Total nap duration, min	59 ± 43	55 ± 77	113 ± 104	n.s.

PH severities are grouped according to hemodynamics in modest (mPAP 26–39 mm Hg), severe (mPAP ≥40 mm Hg) and very severe (mPAP ≥40 mm Hg, with mixed venous oxygen saturation <60%). p values represent main effects by ANOVA: * $p < 0.05$ versus modest and ** $p < 0.05$ versus severe (in post hoc comparisons).

[1] Two patients in functional class IV tended to have syncopies, but their walk distance was relatively well preserved (452 and 464 m, respectively) and one 34-year-old patient in functional class II had a walk distance of 702 m despite hemodynamically very severe PH.

was reduced by a factor of 0.978. In a model including age, gender, mPAP and the New York Heart Association (NYHA) class as covariates, the NYHA class was also an independent predictor of survival (p = 0.033) but the others factors were not (p = 0.24, 0.73 and 0.092). Adding the 6MWT or NT-proBNP as covariates to the regression model did not reveal further significance. Kaplan-Meier analysis did not reveal a significant difference in survival between patients grouped according to the median daytime activity count (p = not significant for the comparison of patients with $>9.5 \times 10^4$ counts vs. $\leq 9.5 \times 10^4$ counts).

Discussion

In this study, we employed wrist actigraphy to assess the 24-h activity patterns of ambulatory patients with pulmonary arterial or chronic thromboembolic PH during a 2-week period of their usual life at home. We found that patients with very severe PH had reduced daytime activity counts and a prolonged nocturnal rest time compared to patients with less severe forms of PH. Daytime activity counts were positively correlated with quality of life in the general health domains. Moreover, follow-up over >4 years revealed that patients with less than 15 h of daytime activity had a shorter transplantation-free survival than patients with longer daytime activity. Actigraphy is simple to perform, is unobtrusive and reflects the patient's activity during daily life at home, so it is a promising novel tool for the assessment of disease severity and prognosis in PH patients.

It is crucial for the potential end points of clinical trials in PH to be clinically relevant, sensitive to treatment effects and easily measurable and interpretable [21]. Actigraphy might have the potential to serve as such an end point for PH studies. Wrist actigraphy is a well-established and validated tool to assess daily activity over longer periods of time [9, 22, 23]. It has been used mainly in sleep medicine, but also to assess daily physical activity in various diseases, such as chronic pain, chronic obstructive pulmonary disease, elevated blood pressure and heart failure [10, 12, 24, 25]. Many reports show that constricted daily activity due to disease is associated with a reduced quality of life and increases the risk of comorbidities occurring such as depression and obesity [26–30]. As a subjective assessment of daily activity in everyday life is not reliable and varies between individuals [30], objectively assessed daily activity by actigraphy is simple, well tolerated and reproducible. Thus, actigraphy has the potential to serve as prognostic and outcome parameter in practice and in scientific trials.

The test most commonly used to investigate exercise performance in PH is the 6MWT [31]. It correlates fairly well with peak aerobic capacity [32] and has been accepted as a clinically relevant trial end point. However, it might be less discerning in the case of patients who are less ill and in patients who are already under maximal therapy with different drugs [21]. In addition, it might not accurately reflect the performance of patients in everyday life. Accordingly, the 3 groups of patients with various PH severities in this study had a similar 6-min walk distance, but differed in their activity patterns recorded by actigraphy over 2 weeks at home (table 3). Global and health-related quality of life measurements are often used to evaluate patients' perception of treatment effects [15, 33]. However, regulatory agencies regard this end point with caution as being too amorphous and inconsistent across different cultures. Actigraphy has advantages over other outcome measures used in patients with PH as it reflects daily activity over longer periods of time in everyday life. In our study, we could demonstrate that patients with a duration of daily activity of less than 15 h had a significantly shorter survival without lung transplantation compared to patients who were more active. In Cox regression models including other potential prognostic variables such as age, gender, the WHO functional class, 6MWT, NT-proBNP and pulmonary artery pressure, daily activity duration remained an independent predictor of survival. The lack of a dependency on age and gender strengthens the use of actigraphy as a tool for the assessment of outcomes in patients with pulmonary arterial or chronic thromboembolic PH. Unlike daytime activity duration, daytime activity counts were not significant predictors of survival. This may relate to the fact that daytime activity duration is not sensitive to acceleration amplitude. Therefore, compared to activity counts, activity duration is less susceptible to variation in the type of activity (e.g. whole body movements vs. arm movements), arm length and type (brand) of actimeter. However, our study was not powered to exclude that actigraphic activity counts might also correlate with survival. Little is known about the prognostic value of actigraphy data in general. Daily activity energy expenditure was strongly associated with a lower mortality in presumably healthy elderly adults [34]. In patients with chronic heart failure, reduced weekly pedometer scores were strong predictors of death whereas symptom-limited office treadmill exercise with two different protocols were not [35]. Consistent with these findings, our data indicate that a relative immobility assessed by actigraphy is associated with a poor prognosis in PH patients. Whether repeated actigraphy during long-term follow-up would help to assess changes in disease activity and guide treatment could not be explored in our study but this does warrant further investigation.

Reduced daily activity counts correlated significantly with hemodynamic disease severity and impaired quality of life in this patient cohort on stable therapy. Patients with severe PH spent more time resting at night and were significantly less active during the day compared to those who were less severely affected. Mean daytime activity duration in our cohort was slightly shorter than previously described in patients with congestive left-heart failure with and without sleep-disordered breathing (14:53 ± 1:10 vs. 16.3 ± 1 and 15.2 ± 1.2 h) [10]. This underscores the severe activity limitation in the everyday life of patients affected by pulmonary arterial or chronic thromoembolic PH [13]. In line with previous studies, more than a third of our patients had sleep-disordered breathing with mainly central apnoea/Cheyne-Stokes respiration and low nocturnal oxygen saturation [14, 36, 37]. However, these disturbances did not result in a subjectively perceived excessive daytime sleepiness. In contrast to patients with left-heart failure, we could not find significant associations of sleep-disordered breathing with daytime actigraphy data in our patients with increased right heart load [10].

In conclusion, if confirmed in larger cohorts, our data suggest that actigraphy is a promising technique for assessing outcome in patients with pulmonary arterial and chronic thromboembolic PH. The correlation of variables derived from actigraphy with disease severity and survival suggest that actigraphy might serve as a valuable tool in future trials in PH.

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Financial Disclosure and Conflicts of Interest

There are no competing interests for any of the authors.

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